Semen Quality in Relation to Biomarkers of Pesticide Exposure

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We previously reported reduced sperm concentration and motility in fertile men in a U.S. agrarian area (Columbia, MO) relative to men from U.S. urban centers (Minneapolis, MN; Los Angeles, CA; New York, NY). In the present study we address the hypothesis that pesticides currently used in agriculture in the Midwest contributed to these differences in semen quality. We selected men in whom all semen parameters (concentration, percentage sperm with normal morphology, and percentage motile sperm) were low (cases) and men in whom all semen parameters were within normal limits (controls) within Missouri and Minnesota (sample sizes of 50 and 36, respectively) and measured metabolites of eight current-use pesticides in urine samples provided at the time of semen collection. All pesticide analyses were conducted blind with respect to center and case–control status. Pesticide metabolite levels were elevated in Missouri cases, compared with controls, for the herbicides alachlor and atrazine and for the insecticide diazinon [2-isopropoxy-4-methylpyrimidinol (IMPY)]; for Wilcoxon rank test, $p = 0.0007$, 0.012, and 0.0004 for alachlor, atrazine, and IMPY, respectively. Men from Missouri with high levels of alachlor or IMPY were significantly more likely to be cases than were men with low levels [odds ratios (ORs) = 30.0 and 16.7 for alachlor and IMPY, respectively], as were men with atrazine levels higher than the limit of detection (OR = 11.3). The herbicides 2,4-D (2,4-dichlorophenoxyacetic acid) and metolachlor were also associated with poor semen quality in some analyses, whereas acetochlor levels were lower in cases than in controls ($p = 0.04$). No significant associations were seen for any pesticides within Minnesota, where levels of agricultural pesticides were low, or for the insect repellant DEET (*N,N*-diethyl-*m*-toluamide) or the malathion metabolite malathion dicarboxylic acid. These associations between current-use pesticides and reduced semen quality suggest that agricultural chemicals may have contributed to the reduction in semen quality in fertile men from mid-Missouri we reported previously. *Key words:* agriculture, pesticides, semen quality, sperm concentration, sperm morphology, sperm motility. *Environ Health Perspect* 111:1478–1484 (2003). doi:10.1289/ehp.6417 available via *http://dx.doi.org/* [Online 18 June 2003]

A study by Nelson and Bunge (1974), noting poor semen quality in fertile men from Iowa City, Iowa, relative to men from New York, concluded,

> Confirmation of our findings would imply that some unknown factor has caused a decrease in male fertility potential as measured by semen analysis.

Although the question of a possible decline in semen quality has been widely studied (Carlsen et al. 1992; Swan et al. 1997), before 2003 no other study included a population drawn from an agrarian environment similar to that of Iowa City to confirm or refute this conjecture. Earlier this year we reported results from the Study for Future Families (SFF), a multicenter study of semen quality in fertile men that included men from mid-Missouri, an area comparable demographically and agriculturally with Iowa City (Swan et al. 2003). Iowa City, Iowa, like Columbia, Missouri, has more than 50% of county acreage in farms, and both are located in counties in which pesticide use is high (U.S. Census Bureau 2001).

In SFF we found, as had Nelson and Bunge (1974), reduced sperm concentration and motility in men from a U.S. agrarian area (Columbia, MO) relative to men from U.S. urban centers: Los Angeles, California; Minneapolis, Minnesota; and New York, New York. Unlike earlier studies, tight quality control and standardization of all study methods made it unlikely that the variation in semen quality we observed was attributable to differences in laboratory or recruitment methods. We examined multiple potential confounders, and results were largely unchanged after statistical adjustment for these factors. Therefore, we sought to identify environmental agents associated with these between-center differences in semen quality. We hypothesized that pesticides used widely in mid-Missouri, and rarely in urban areas, might have contributed to the poor semen quality seen in men from mid-Missouri, and perhaps shed light on the finding of Nelson and Bunge (1974). In this article, we follow common use and apply the term "pesticide" not only to insecticides but also to a variety of other agricultural chemicals, including herbicides, fungicides, and various other pest control substances [U.S. Environmental Protection Agency (U.S. EPA) 1997].

It is well known that exposure to pesticides at occupational levels can adversely affect semen quality. In the late 1970s the nematocide dibromochloropropane affected more than 26,000 plantation workers in 12 countries; 64% had low sperm concentrations and 28% were involuntarily childless (Goldsmith 1997; Slutsky et al. 1999; Thrupp 1991). The chlorinated hydrocarbon pesticide chlordecone (kepone) was withdrawn in 1975 because of oligozoospermia and decreased motility resulting from occupational exposures (Faroon et al. 1995). Ethylene dibromide was an active component of approximately 100 pesticides. Its use was severely restricted in 1984 because of reduced sperm counts and semen volume in exposed workers (Schrader et al. 1988; Whorton 1981). More recently, a small study of herbicide sprayers in Argentina showed decreased sperm concentration and morphology related to high urinary levels of 2,4-D (2,4-dichlorophenoxyacetic acid) metabolites (Lerda and Rizzi 1991). Greenhouse workers in Denmark with greater/longer pesticide exposure had lower sperm counts and percentages of morphologically normal sperm (Abell et al. 2000). After a report of high sperm counts in organic farmers in Denmark, a series of studies were designed to compare reproductive health between traditional and organic farmers. Although questionnaire data showed

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